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14. ABSTRACT

The current proposal aims to directly compare the psychotherapy and medication treatments for PTSD considered to have the most evidence for effectiveness. While both SSRI and PE have demonstrated efficacy, there are significant individual differences in clinical responses to both treatments. To achieve best clinical outcomes and to utilize available treatment most effectively, it is critical to examine how PTSD and related psychopathology and functional impairment change with these treatments alone and in combination. Further, in order to inform clinical practice, we plan to examine psychological and neurobiological predictors of response to treatment and mechanisms of change during treatment (pre to post treatment change) based on previously identified predictors, including emotion regulation and processing with fMRI in response to emotional challenge tasks, DNA (pre treatment only) and mRNA (pre and post treatment), and cortisol response to awakening.

15. SUBJECT TERMS
PTSD, sertraline, prolonged exposure, randomized control trial, OEF/OIF/OND, veterans

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INTRODUCTION

PTSD is a major public health concern and a growing problem for the VA and the DOD [1, 2]. Soldiers returning from Afghanistan and Iraq show PTSD rates of between 12 to 20% [3-6] with significant psychological, physical, and economic burdens for sufferers and society as a whole [7, 8]. Based on available treatment guidelines [9], the two first line treatments for PTSD include exposure therapy (such as PE) and selective serotonin reuptake inhibitors (SSRIs; such as SERT). To date, there have been no randomized, direct, comparisons of medication, psychotherapy, and combined treatment among veterans or active duty troops. The current study aims to provide this critical data in a typical sample of OEF/OIF returnees with significant combat-related PTSD. Further, emphasis is placed on continued, comprehensive, collection of outcome data to assess the acceptability, adherence, compliance, and symptom change in each treatment arm throughout the study period. In addition, substantial morbidity remains in a high percentage of PTSD veterans [10, 11] even after PE or SSRI treatment are administered, suggesting that further treatment optimization and individual treatment matching are urgently needed if substantial personal and social costs are to be reduced. Identifying specific predictors, large effect size correlates of treatment response, or putative mechanisms involved in treatment response will be critical steps toward achieving the goals of treatment optimization and individual treatment matching. To inform treatment choices beyond what can be provided through standard clinical outcomes, we will examine neurobiological predictors and proximal correlates of effective treatment, and candidate mechanisms involved. Delineation of these factors and their specificity to medication or PE is a critical step towards treatment refinements, improved effectiveness and efficiency of PTSD treatment, enhanced dissemination, and individualized treatment. This is obviously an ambitious set of goals; however, the combined expertise of the research group involved, the synergy of the aims, and the efficient design, offer both a unique opportunity to examine multiple processes simultaneously, and to obtain the highest quality of critically needed data. To restrict the examination to just one system or one mechanism would be a missed opportunity to study these complex and interrelated systems, and their interacting in impacts on treatment.

BODY

This project will consist of seven primary tasks to be accomplished over the 5 year funding period at four sites: Veterans Affairs Ann Arbor Healthcare System (VAAAHS) /University of Michigan (UM), VA San Diego Healthcare System (VASDHS)/University of California San Diego (UCSD), VA Charleston VA Medical Center (VAMC)/ Medical University of South Carolina (MUSC), and Massachusetts General Hospital (MGH)/Harvard Medical School.

Task 1: Start-up activities and regulatory approvals (first 6 months)

- **Obtained Full approval at VA Ann Arbor Healthcare System, University of Michigan, and HRPO**
- **Deliverables to date (e.g., protocol, IRB, publications, presentations, etc.)**
    - Primary Site (VAAAHS/UM) received approval by the Ann Arbor VA Human Studies Committee on November 10, 2010 and the Biosafety Subcommittee on

October 21, 2010 and received final approval from the Ann Arbor VA Research and Development Committee on December 1, 2010. The University of Michigan IRB granted approval on December 2, 2010. Final approval from HRPO was granted on June 21, 2011. Recruitment started December 12, 2011.

- MGH received approval from the MGH Radiation Safety Committee on July 20, 2011, and received approval from the MGH Clinical Trials Pharmacy Committee on August 9, 2011. Initial IRB Approval from the Partners Human Research Committee was received on August 19, 2011. Final approval from HRPO was granted on September 8, 2011. Recruitment started on November 29, 2011.
- MUSC and VASDHS/UCSD have full local IRB approval
  - VASDHS/UCSD is pending VA R& D and final HRPO approval which should be granted in January 2012. Expected recruitment start date is January 2012
  - MUSC is received approval from the MUSC IRB on July 5, 2011, the VA Biosafety Subcommittee on August 2, 2011, and the VA R&D Committee on August 24, 2011. Final approval from HRPO is still pending, but expected by the end of December 2011. Excepted recruitment start date is February 2012

- **All sites have key positions hired in order to begin recruitment.**
- **Payment processes in place and being fulfilled in a timely manner.**
- **Subawards completed**

<u>Task 2:</u> Training of study faculty and staff (first 6 months)

- **All key study personnel have been trained in order to start recruitment**
  - VAAAHS/UM is currently in the process of hiring1 Fidelity Rater and 1 Nurse Practitioner
  - VASDHS/UCSD is currently in the process of hiring 1 Fidelity Rater and may still hire an additional Pharmacotherapist
  - MUSC hired 1 additional Research Assistant, Michelle Pompei, who will start January 3, 2012, but this will not prevent the start of recruitment
  - Dr. Steven Buffo was also added as a Pharnacotherapist at the MUSC site in December 2011
- **Study Team assemble and meet every week via Conference Call**
  - The calls alternate between PI/ CoIs/Study Coordinators and only Study Coordinators meeting with Lead Site PI and Lead Study Coordinator via conference call
  - Dr. Mark Pollack was removed from the study due to leaving the MGH site and Dr. Brian Martis was added as co-Investigator and Psychopharmacology lead for Ann Arbor
- **Work through logistics, set-up and planning**
  - Therapist didactic training complete and cases nearly complete, with only MUSC remaining. Completion expected February 2012.
  - Initial Pharmacotherapist training completed in October 2011 with monthly follow-up calls scheduled to answer questions
  - Evaluator training completed in November 2011, Q&A call completed in November 2011

- fMRI paradigm ready for execution
- Pharmacies established and medication compounding processes complete
- Study Kick Off Meeting held Sept 19-20th in Charleston, SC was successful – key study personnel trained in all relevant study procedures

<u>Task 3:</u> Set up study forms and refine all procedures

- All study forms complete – CRF distribution is currently ongoing with paper version of CRFs available for download and printing at each site. CRF binders have been disseminated by primary site
- Velos measures complete
- Laboratory procedures finalized – supplies ordered and shipments sent to sites for initial recruitment
- fMRI protocol finalized
- All procedures finalized

<u>Task 4:</u> Recruit and randomly assign Operation Enduring Freedom/Operation Iraqi Freedom/ Operation New Dawn(OEF/OIF/OND) returnees with combat related Posttraumatic Stress Disorder (PTSD) to PE+ placebo (PE/PLB), sertraline + enhanced medication management (SERT), or PE + sertraline (PE/SERT)

- Two sites have begun recruitment with no patients enrolled yet
  - MGH started recruitment on November 29, 2011
  - VAAAHS/UM started recruitment on December 12, 2011
- The remaining two sites, MUSC and VASDHS/UCSD expect to start recruitment in early 2012
  - MUSC is awaiting final approval from HRPO which is expected by the end of December 2011 and has 1 Prolonged Exposure Therapy Provider finishing training by February 2012
  - VASDHS/UCSD is awaiting approval from the VA R&D committee and final approval from HRPO. Both approvals are expected by January 2012

<u>Task 5:</u> Conduct neurobiological mechanism study including assessment of genetics/genomics, brain function (first 210 interested participants), and hypothalamic–pituitary–adrenal (HPA) axis function

- fMRI protocol finalized
- Travel logistics nearly complete, expected completion by end of December 2011

Task 6) Follow-up of all returnees for one year from treatment initiation.
Not applicable for this reporting period

Task 7) Data cleaning, initial statistical analyses and dissemination of results.
Not applicable for this reporting period

Delays/Challenges/Barriers

- Study startup has been delayed numerous times. Primary causes included:

    - Waiting for approvals on documents at all the respective sites. Amending documents must be done and approved at each site – usually having to receive approval by 2 IRBs. This becomes a timely process
    - Only two sites are waiting for final HRPO approval and this should be completed by January 2012
    - Hiring – delays in getting some positions filled. All sites have the key positions hired with some additional hiring and training required to get to full capacity
- MUSC site did not have non-cycling freezer access. They purchased a new freezer on December 1, 2011

KEY RESEARCH ACCOMPLISHMENTS

Not applicable this reporting period

REPORTABLE OUTCOMES

Not applicable this reporting period

CONCLUSION

Not applicable this reporting period

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APPENDICES

Not applicable this reporting period